



Escitalopram Tablets

NDA # 21-323

Patent Information

**APPEARS THIS WAY
ON ORIGINAL**



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Patent Number: Re. 34,712

Boegesoe et al.

[45] Reissued Date of Patent: Aug. 30, 1994

[54] PHARMACEUTICALLY USEFUL
(+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-
FLUOROPHENYL)-1,3-DIHYDROISO
BENZOFURAN-5-CARBONITRILE AND
NON-TOXIC ACID ADDITION SALTS
THEREOF

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[21] Appl. No.: 122,009

[22] Filed: Sep. 14, 1993

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 4,943,590
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[30] Foreign Application Priority Data

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[51] Int. Cl.⁵ A61K 31/34; C07D 307/87;
C07C 255/59

[52] U.S. Cl. 514/469; 549/467;
558/422

[58] Field of Search 549/467; 558/422;
514/469

[56] References Cited

U.S. PATENT DOCUMENTS

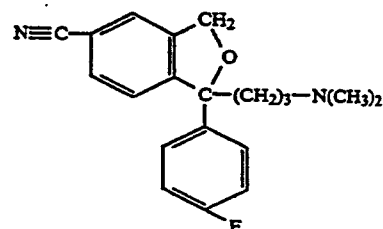
4,136,193 1/1979 Boegesoe et al. 549/467
4,650,884 3/1987 Boegesoe 549/467

Primary Examiner—Bernard Dentz

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] ABSTRACT

The two enantiomers of the anti-depressant drug of the
formula I



are disclosed. Methods for resolving intermediates and
their [stereoselective] stereoselective conversion to a
corresponding [enantiomer] enantiomer of I are also
disclosed.

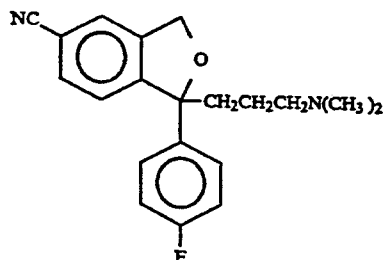
12 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

PHARMACEUTICALLY USEFUL
(+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-
FLUOROPHENYL)-1,3-DIHYDROISO
BENZOFURAN-5-CARBONITRILE AND
NON-TOXIC ACID ADDITION SALTS THEREOF

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylamino-propyl)-1-(4'-fluorophenyl)-1,3-**[dihydroisobenzofuran]** *dihydroisobenzofuran*-b 5-carbonitrile (citalopram) of the following formula I:



and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or **[dichloromethane]** *dichloromethane*, with the desired salt separating directly. Exemplary of such organic **[salt]** *salts* are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halothephyllines, for example 8-bromothephylline.

Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Furthermore it was found that non-hygroscopic acid addition salts might be obtained by **[conventional]** *conventional* freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

The invention is also concerned with a method to resolve the intermediate racemate and to produce the individual isomers of I therefrom.

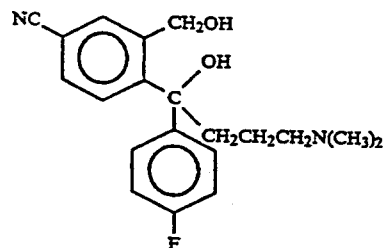
BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in e.g. U.S. Pat. No. 4,136,193, has proven to be an efficient antidepressant

sant compound in man (Ref.: A. Gravem et. al., Acta psychiatri. Scand., No. 75, p. 478-486 (1987). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

SUMMARY OF THE INVENTION

Surprisingly, it has now proven possible to resolve the intermediate **[4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile]** *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of II formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a stereoselective ringclosure reaction. The intermediate diol, II, has been disclosed in e.g. U.S. Pat. No. 4,650,884 as a racemic mixture.



The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

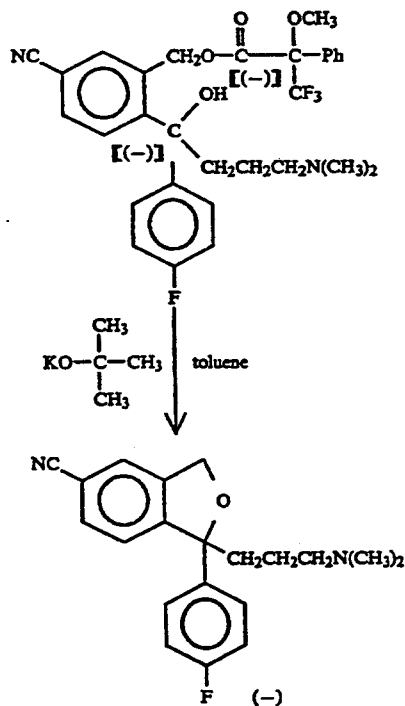
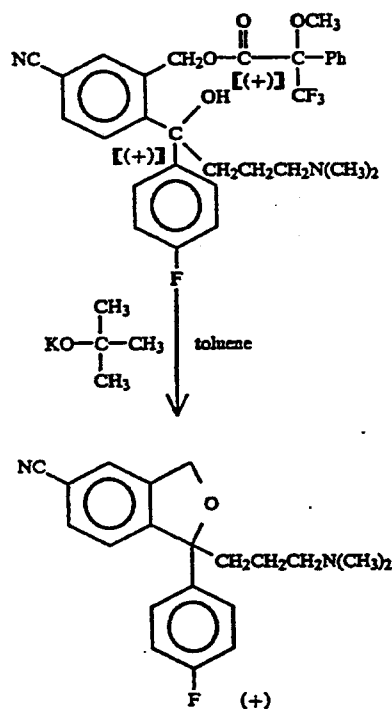
According to the invention, II is reacted with:

(a) an enantiomerically pure acid derivative as an acid chloride, anhydride or **[labile]** *labile* ester as e.g. **[exemplified]** *exemplified* in reaction scheme I by (+)- or (-)- α -methoxy- α -trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as e.g. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsequently separated by HPLC or fractional crystallization. The thus purified **[diastereoisomers]** *diastereoisomers* are **[finally]** *finally* separately treated with strong base (e.g. alkoxide) in an inert organic solvent as e.g. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at

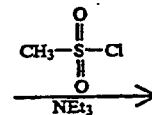
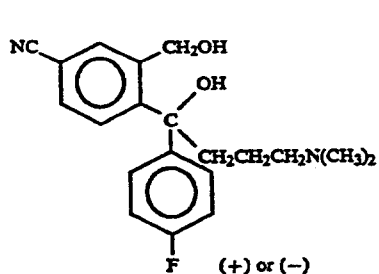
REACTION SCHEME II

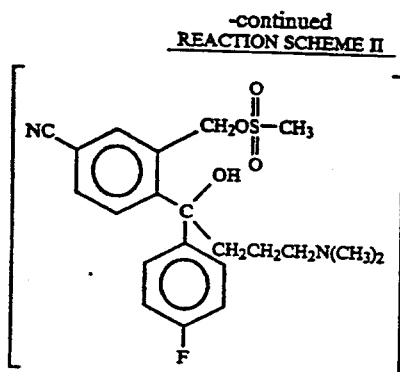
N#Cc1ccc(cc1)C(O)(CO)c2ccc(F)cc2

(2) HPLC separation



(c) Stereoselective ringclosure of the pure enantiomers of II prepared as in (b) is performed via a labile ester as e.g. methansulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethansulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridine) in an inert organic solvent at 0° C. The ringclosure reaction is [exemplified] *exemplified* in reaction scheme II:





EXAMPLE 1

Resolution by method (a)

To 11 g of (+)-α-methoxy-α-trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)-α-methoxy-α-trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of [4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried (MgSO₄) and the solvent evaporated below 30° C. in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated HPLC purification (eluted with ethyl acetate/tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5-10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0° C. The toluene solution was washed with water, dried (MgSO₄) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D^{25} = +11.81^\circ$ (c=1, CH₃OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ¹H NMR spectroscopy (CDCl₃ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihy-

droisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D^{25} = -12.34^\circ$ (c=1, CH₃OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.0%.

EXAMPLE 2

Resolution by methods (b) and (c)

To a solution of 85 gr of [4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2M NaOH solution and 500 ml of ether. The mixture was stirred for ½ hour, the ether phase separated, dried (MgSO₄) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at 40° C., and 40 gr of (+)-di-p-[toloyltartaric] toluoyltartaric acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of [(-)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] (-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)benzonitrile, hemi (+)-di-p-[toloyltartaric] toluoyltartaric acid salt. MP: 134°-135° C., $[\alpha]_D^{25} = +10.0^\circ$ (c=1, CH₃OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (-)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for ½ hour, washed with brine, dried (MgSO₄) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl) fluorophenyl-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D^{25} = +12.33^\circ$ (c=1, CH₃OH). The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147°-148° C., $[\alpha]_D^{25} = +12.31^\circ$ (c=1, CH₃OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently cooled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt. MP: 264°-266° C., $[\alpha]_D^{25} = +13.88^\circ$ C. (c=1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The water-phase was freeze-dried in vacuo (<0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] (+)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, hemi (-)-di-(p-toloyl)-tartaric acid salt ($[\alpha]_D^{25} = -8.9^\circ$ (c=1, CH₃OH)) which was converted to the corresponding diol base ($[\alpha]_D^{25} = +61.1^\circ$ (c=1, CH₃OH)) and finally ringclosure

reaction yielded 10 gr of (-)-1-(3-dimethylamino-propyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1^\circ$ ($c=1$, CH_3OH).

The oxalic acid salt of the (-)-isomer crystallized from acetone, MP: $147^\circ\text{--}148^\circ\text{C}$, $[\alpha]_D = -12.08^\circ$ ($c=1$, CH_3OH).

EXAMPLE 3

Preparation of citalopram by method (c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methansulfonyl chloride in 30 ml of dichloromethane were added dropwise during a half hour. The reaction mixture was washed with 0.1M NaOH solution twice, the organic phase separated, dried (MgSO_4) and the solvent evaporated, leaving 21.5 gr of the title (\pm)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP $184^\circ\text{--}186^\circ\text{C}$.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsøe and Svendsen; European J. Pharmacol. 41, 153-162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and 5-HTP is used as reference for full 5-HT syndrome.

The Route of Administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: (1) excitation, (2) tremor, and (3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, ... 9/9, where 0, 1, ..., 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^3H -SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of [^3H -serotonin] ^3H -serotonin (^3H -5-HT)(10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13-18; Hyttel, Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1982, 6, 277-295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146-153. [Procedure p]

Procedure

Male Wistar (Mol: Wist) rats (125-250 g) are sacrificed by decapitation and [exanguinated] *exsanguinated* Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of ice cold 0.32M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g. 10 min and 25000 g. 55 min, 4°C .) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 μl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 μl test substance in water. After preincubation at 37°C . for 5 min, 100 μl of ^3H -1-NA (final [concentration] concentration 10 nM) are added and the samples are incubated for 10 min at 37°C . The incubation is terminated by filtering the samples under vacuum through [Whatman] *Whatman* GF/F filters with a wash of 5 ml buffer containing 10 μM of unlabeled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor @15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 μM citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC_{50} -value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 μM of citalopram.

TABLE 1

| PHARMACOLOGICAL TEST RESULTS | | |
|------------------------------|--|--|
| Compound | 5-HTP pot. ED_{50} $\mu\text{mol/kg}$ | 5-HT uptake inhibition IC_{50} (nM) |
| (+)-citalopram | 2.0 | 1.1 |
| (-)-citalopram | 120 | 150 |
| (\pm)-citalopram | 3.3 | 1.8 |

(+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheep or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, [capsles] *capsules*, powders, syrups or in the form of the usual [sterial] *sterile* solutions for injection. [Results upon administration to human being have been very gratifying.]

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said compounds in [a] *an* amount of from about 0.10 to about 100 mg, most preferably, however, from about 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the [active] active ingredient is for the most part mixed with ordinary tablet adjuvants such as corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, or the like.

Typical examples of formulas for [composition] compositions containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

(1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:

| | |
|--------------------|--------|
| Compound 20 | 5 mg |
| Lactose | 18 mg |
| Potato starch | 27 mg |
| Saccharose | 58 mg |
| Sorbitol | 3 mg |
| Talcum | 5 mg |
| Gelatine | 2 mg |
| Povidone | 1 mg |
| Magnesium stearate | 0.5 mg |

(2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:

| | |
|--------------------|--------|
| (+)-citalopram | 50 mg |
| Lactose | 16 mg |
| Potato starch | 45 mg |
| Saccharose | 106 mg |
| Sorbitol | 6 mg |
| Talcum | 9 mg |
| Gelatine | 4 mg |
| Povidone | 3 mg |
| Magnesium stearate | 0.6 mg |

(3) Syrup containing per milliliter:

| | |
|----------------|----------|
| (+)-citalopram | 10 mg |
| Sorbitol | 500 mg |
| Tragacanth | 7 mg |
| Glycerol | 50 mg |
| Methyl-paraben | 1 mg |
| Propyl-paraben | 0.1 mg |
| Ethanol | 0.005 ml |
| Water ad | 1 ml |

(4) Solution for injection containing per milliliter:

| | |
|------------------|---------|
| (+)-citalopram | 50 mg |
| Acetic acid | 17.9 mg |
| Sterile water ad | 1 ml |

(5) Solution for injection containing per milliliter:

| | |
|------------------|---------|
| (+)-citalopram | 10 mg |
| Sorbitol | 42.9 mg |
| Acetic acid | 0.63 mg |
| Sodium hydroxide | 22 mg |
| Sterile water ad | 1 ml |

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bismethylenesalicylic, propionic, gluconic, malic,

malonic, mandelic, [cannamic] cinnamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may [be] also be employed as acid addition salt-forming acids.

When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic [solvent] solvent, drying the extract and evaporating to dryness or fractionally distilling to effect isolation of the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological [abnormalities] abnormalities of animals, especially depressions, by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

It is to be understood that the invention is not limited to the exact details of operation or exact [compound] compounds or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

We claim:

1. A compound selected from substantially pure (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

2. A compound of claim 1 being the pamoic acid salt of substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

3. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, a compound as defined in claim 1.

4. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, the compound of claim 2.

5. A pharmaceutical composition in unit dosage form, according to claim 3, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

6. A pharmaceutical composition in unit dosage form, according to claim 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

7. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 1 which is effective for said purpose.

8. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 2 which is effective for said purpose.

9. Method of claim [10] 7 wherein the compound is administered in the form of a pharmaceutical composition thereof.

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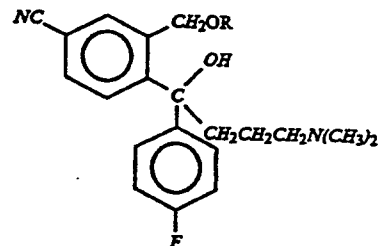
10. Method of claim 8 wherein the compound is administered in the form of a pharmaceutical composition thereof.

11. A method for the preparation of a compound as defined in claim 1, which comprises, converting substantially, pure [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] (-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile or a [monomester] monoester thereof in a stereoselective way to substantially pure (+)-1-(3-dimethylamino-propyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

12. A compound of the formula (3I)-Enantiomer of the compound 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-

12

1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile or an ester of said (-)enantiomer, which has the formula



15 wherein R is hydrogen or represents a group completing a labile ester.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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DATED : August 30, 1994

Page 1 of 2

INVENTOR(S) : Klaus Boegesoe, Jens K. Perregaard

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 40; "ageuous" should read -- aqueous --

Column 1, line 43; "[salt]" should read -- [salt] --

Column 2, line 2; "Scan.," should read -- Scand., --

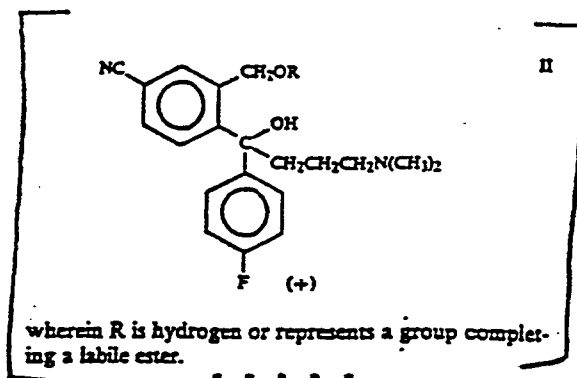
Column 4, line 1; move the words "REACTION SCHEME II" down to line 55 to be together with the formulae which follow.

Column 6, line 4; "99.0%" should read -- 99.9% --

Column 7, line 62; "(10 nm)" should read -- (10 nM) --

Column 11, line 16; Before "12." insert a bold -- [-- and after the word "formula" insert a bold --] --

Column 11, line 16; After "formula" and Before "(31)" insert the following.



UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : Re. 34,712

DATED : August 30, 1994

Page 2 of 2

INVENTOR(S) : Klaus Boegesoe, Jens K. Perregaard

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 11, lines 16 and 17; delete the rest of this line
16, namely: "(31)-Enantiomer of" and delete line 17 and
rewrite in *italics* as lines 40 and 41 as follows:
-- 12. (-) - Enantiomer of the compound
4-[4-(dimethylamino)-1-(4'-fluorophenyl)- --

Column 12, lines 15 & 16 should be in *italics*.

Signed and Sealed this
Second Day of January, 1996

Attest:



BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks



Escitalopram Tablets

NDA # 21-323

Debarment Certification

**APPEARS THIS WAY
ON ORIGINAL**



FAX: 212-750-9752

PHONE: 212-421-7850

DEBARMENT CERTIFICATION

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food and Cosmetic Act in connection with this application (NDA #21-323) for escitalopram.

FOREST LABORATORIES, INC.

A handwritten signature in cursive script, appearing to read 'L. Olanoff', is written over a horizontal line.

Lawrence Olanoff, M.D., Ph.D.
Executive Vice President, Scientific Affairs

A handwritten date '3/5/01' is written over a horizontal line.

Date

FOREST LABORATORIES, INC.
909 Third Avenue
New York, NY 10022-4731



Escitalopram Tablets

NDA # 21-323

User Fee Form

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311-3988

3. PRODUCT NAME

Escitalopram Oxalate Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(201) 386-2126

5. USER FEE I.D. NUMBER

4035

6. LICENSE NUMBER / NDA NUMBER

21-323

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT
FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT
LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Manager, Regulatory Affairs

DATE

March 1, 2001



FAX: 201-524-9711

Phone: 201-386-2126

March 1, 2001

Food and Drug Administration
Mellon Bank/FDA (360909)
Three Mellon Center, 27th Floor
Pittsburgh, PA 15259-0001

Re: NDA 21-323, User Fee
User Fee # 4035

Product: Escitalopram Oxalate 5, 10 & 20 mg Tablets

To whom it may concern:

In accordance with the Federal Register Notice of December 18, 2000, a check for the amount of \$309,647.00 (check #353050) is being paid for the new drug application for Escitalopram Oxalate 5, 10 & 20 mg Tablets, NDA #21-323, which will be submitted in March, 2001.

If you have any questions regarding this material, please call me at 201-386-2126.

Thank you for your time and consideration. If there are any questions related to this NDA, please contact me at (201) 386-2126 or in my absence Brian Wildstein at (201) 386-2115.

Sincerely,

Daniel T. Coleman, Ph.D.
Manager, Regulatory Affairs

FOREST LABORATORIES, INC.
PLAZA THREE, SUITE 602

HARBORSIDE FINANCIAL CENTER
JERSEY CITY, NJ 07311



Escitalopram Tablets

NDA # 21-323

Financial Disclosure

**APPEARS THIS WAY
ON ORIGINAL**

Financial Disclosure:

Financial disclosure is reported for all investigators for all studies relied on to support the safety and efficacy of escitalopram covered by 21 CFR part 54. The attached Form FDA 3454 indicates that the applicant (Forest Laboratories, Inc.) is the sponsor of some of the studies submitted in this application and that a list of investigators who had no disclosable financial arrangements is attached (Attachment 1).

Some studies in this application were sponsored by H. Lundbeck. H. Lundbeck has informed Forest that there were no disclosable financial arrangements between H. Lundbeck and any of the investigators on their studies. Form 3454 therefore also indicates that some of the studies were conducted by a sponsor (H. Lundbeck) other than the applicant and that a list of investigators who had no disclosable financial arrangements is attached (Attachment 2).

Financial disclosure could not be obtained for some investigators on Forest sponsored studies despite repeated attempts by Forest and the sites involved. Form 3454 therefore also indicates that a list of investigators who did not disclose their financial arrangements is attached (Attachment 3). Investigators included in this list were all subinvestigators and the vast majority had participated in the early stages of the study. When attempts were made to contact these investigators (who had already left the sites) the investigators could no longer be reached.

There were six investigators who did have financial arrangements that required disclosure. All of these investigators were participants in studies SCT-MD-01 or SCT-MD-02. A description of each investigator's relevant financial arrangements and a Form 3455 is provided for each such investigator.

Although some investigators participating in covered studies in this NDA had disclosable financial arrangements, the potential of these financial arrangements to bias the studies is minimized by the following elements of the design and conduct of Studies SCT-MD-01 and SCT-MD-02. Both studies were:

1. Double blind
2. Placebo- and active-controlled
3. Multi-centered with multiple investigators at each site.
4. In many cases the data for individual subjects were collected by multiple investigators at multiple visits.
5. The sites were independently monitored.
6. The sites were randomly audited by Forest Laboratories, Inc..
7. The sites were inspected, reviewed and supervised by IRBs.
8. The effect of the data from each site on the overall study outcome was analyzed.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

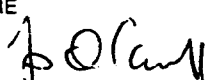
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| | | |
|------------------------|--------------------|--|
| Clinical Investigators | See attached Lists | |
| | | |
| | | |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| | | | | |
|---|--|--------|--|--|
| NAME | TITLE | | | |
| Lawrence Olanoff, M.D. Ph.D. | Executive Vice President Scientific Affairs | | | |
| FIRM/ORGANIZATION | | | | |
| Forest Laboratories Inc. | | | | |
| SIGNATURE | | DATE | | |
|  | | 3-5-01 | | |

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages
Redacted 19



Confidential,
Commercial Information

Disclosable financial Arrangements

Form 3455 and financial Disclosure statements are attached for the six investigators who had financial arrangements to disclose. These investigators were all participants in either Study SCT-MD-01 or SCT-MD-02.

**APPEARS THIS WAY
ON ORIGINAL**

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT


The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator
Name of clinical study

Please mark the applicable checkboxes.

- ☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- ☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- ☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;
- ☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | |
|--|---|
| NAME Lawrence Olanoff, M.D., Ph.D. | TITLE Executive Vice President Scientific Affairs |
| FIRM/ORGANIZATION Forest Laboratories, Inc. | |
| SIGNATURE  | DATE 3-5-01 |

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.


any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | | |
|---|--|--------|
| NAME | TITLE | |
| Lawrence Olanoff, M.D., Ph.D. | Executive Vice President Scientific Affairs | |
| FIRM/ORGANIZATION | | |
| Forest Laboratories, Inc. | | |
| SIGNATURE | | DATE |
|  | | 3-5-01 |

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Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____

Name of clinical investigator

Name of

SCT-MD-01, is submitted in accordance with 21 CFR part
clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.


☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | | |
|---|--|--------|
| NAME | TITLE | |
| Lawrence Olanoff, M.D., Ph.D. | Executive Vice President Scientific Affairs | |
| FIRM/ORGANIZATION | | |
| Forest Laboratories, Inc. | | |
| SIGNATURE | | DATE |
|  | | 3-5-01 |

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Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part _____.

SCT-MD-01 _____, is submitted in accordance with 21 CFR part _____.

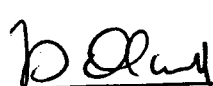
clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- ☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- ☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- ☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;
- ☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | | |
|---|--|--------|
| NAME | TITLE | |
| Lawrence Olanoff, M.D., Ph.D. | Executive Vice President Scientific Affairs | |
| FIRM/ORGANIZATION | | |
| Forest Laboratories, Inc. | | |
| SIGNATURE | | DATE |
|  | | 3-5-01 |

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Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of clinical study

Please mark the applicable checkboxes.


☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | |
|---|--|
| NAME | TITLE |
| Lawrence Olanoff, M.D., Ph.D. | Executive Vice President Scientific Affairs |
| FIRM/ORGANIZATION | |
| Forest Laboratories, Inc. | |
| SIGNATURE | DATE |
|  | 3-5-01 |

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____

Name of clinical investigator

Name of

clinical study SCT-MD-02 _____, is submitted in accordance with 21 CFR part

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.


any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | |
|--|---|
| NAME Lawrence Olanoff, M.D., Ph.D. | TITLE Executive Vice President Scientific Affairs |
| FIRM/ORGANIZATION Forest Laboratories, Inc. | |
| SIGNATURE  | DATE 3-5-01 |

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
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5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages
Redacted 98



Draft Labeling
(not releasable)

Table of Contents
Approvable Package
Lexapro (escitalopram oxalate) Tablets
NDA 21-323

UF DUE DATE Wednesday January 23, 2001

SECTION

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- B: Supervisory Overview: Division Director's Memo**
- C: Group Leader's Memo**

- D: NDA Action Package Checklist**
- E: Exclusivity Checklist**
- F: Pediatric Checklist**

- G: Patent Information**
- H: Debarment Statement**
- I: User Fee Information**
- J: Financial Disclosure Information**

- K: Current Celexa Labeling (Deemed Acceptable in an Acknowledge/Retain Agency Letter Date 5-25-01)**
- L: 1) Prescriber Labeling Proposed by Sponsor in Submission Dated 3-23-01**
2) Annotated Labeling Submitted with 7-12-01 Safety Update
3) Annotated Labeling Submitted with 10-19-01 Safety Update

- M: NDA Submission Chronology (from sponsor)**
- N: Agency Correspondence - Memos/Telecons to the File/Faxes/Meeting Minutes**
- O: Agency Correspondence - Letters**

- P: Clinical Review #1 and #2**
- Q: Statistical Review**
- R: Pharm/Tox Review**
- S: OCPB Review**
- T: CMC Review: #1 and #2, and EER Summary Report**
- U: DSI Reviews**
- V: OPDRA Review**

David, Paul A

From: David, Paul A
Sent: Friday, November 30, 2001 1:08 PM
To: Daniel. Coleman (E-mail)
Cc: David, Paul A
Subject: Escitalopram QT data request NDA 21-323

Dan,

I am attaching a request for information regarding the QT data for escitalopram. The attachment also includes the Division's QT recommendations document that is referred in our request for information.

If you have any questions, please contact me.
Paul



QT information request
for For...



qt recs.pdf

**APPEARS THIS WAY
ON ORIGINAL**

QT information request for Forest re: escitalopram

Although the summary data for change of QTc from baseline for the pooled depression studies as shown in Panel 31 (p.79) of the 120-day Update does not suggest a QTc-prolonging effect of escitalopram (PBO 0.8 msec v. ESCIT 2.0 msec v. CIT 1.6 msec), other data included in the submission raise the possibility that escitalopram (and citalopram) may have the ability to prolong the QT interval. For example, the multiple dose clinical pharmacology study 98107 showed a mean change in QTc from baseline to last dose of 11 msec for escitalopram 30 mg and 10 msec for citalopram 60 mg. As such, we have the following information requests:

1. For each of the studies (clinical pharmacology and phase II/III) in which ECGs were collected, provide the following information:
 - On which visit days were ECGs performed?
 - Were ECGs timed to correlate with T_{max}, or another specific time point following dose administration?
 - Describe the method by which the ECGs were read (e.g., site investigator read, site cardiologist read, central cardiologist read, etc.).
 - If a central cardiologist read the ECGs, were they hand read off a paper copy or read off a digitized version?
 - What method was used to correct the QT interval for heart rate?
2. The escitalopram NDA heart rate data and ECG ventricular rate data suggest that escitalopram and citalopram have a small but consistent bradycardic effect. For drugs that cause bradycardia, Bazett's correction for the QT interval may minimize the degree of QT prolongation. We request that you repeat your QTc analyses following correction of the QT data using Fridericia's method (QT/cube root of the RR interval). In addition, you may choose to calculate a correction factor based on your baseline or placebo data (see attached copy of division recommendations for QT correction) and apply it to the uncorrected QT.
3. In Attachment 5 of the September 27, 2001 submission, Table 1 lists the patients with normal screening ECGs and abnormal ECGs at endpoint.
 - Please provide your definition of the terms "QTcB dispersion prolonged" and "QTcB
 - Certain of these abnormality descriptions are marked as "clinically significant". What were the criteria for clinical significance?
 - Table 2 "Incidence of ECG Abnormalities ($\geq 1\%$ in active treatment group) at Endpoint" appears to have been mistakenly left out of the archival and desk copies of the submission. Please include this table in the new submission. It would be useful if you only included treatment-emergent ECG abnormalities. Please also include the incidence of ECG abnormalities among the active control and placebo control groups.
4. Please submit a discussion of any postmarketing reports that you have received describing QT or QTc prolongation, torsades de pointes, ventricular tachycardia, or

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from the
Original
Approval Package

1 page

Division of Neuropharmacological Drug Products
Recommendations for QT interval correction (revised December 2000)

QT interval length decreases with increasing heart rate. Use of a method of adjusting the QT interval length for heart rate allows the QT interval length to be considered independent of the heart rate at which it was observed.

Direct adjustment of the QT interval for heart rate by dividing the QT length by the square root of the RR interval ($QTc^{SR} = QT/RR^{.5}$), a method first proposed by Bazett in 1920 and the one most commonly used today, clearly results in substantial bias. For heart rates greater than 60, the QTc^{SR} overcorrects the QT interval whereas it undercorrects for rates less than 60. Hence, when exploring the QTc^{SR} data for a drug that increases the heart rate, there would appear to be a dose dependency for the QTc^{SR} even if the drug had no effect on cardiac repolarization. At the same time, correction with Bazett's method could mask QT interval prolongation with a drug that causes bradycardia.

The potential bias from using the square root adjustment has been well described in the literature with many authors proposing alternative methods of adjustment. The cube root correction ($QTc^{CR} = QT/RR^{.33}$), first proposed by Fridericia, can also produce a systematic bias, but the degree of bias is much smaller than Bazett's method and goes in the opposite direction. Both biases appear to be independent of age.

Since Bazett's correction, or $QTc^{SR} = QT/RR^{.5}$, greatly overcorrects for rates greater than 60 and Fridericia's correction, or $QTc^{CR} = QT/RR^{.33}$, slightly undercorrects, we have explored corrections that use slightly larger fractional exponents than 1/3. As it turns out, the model, $QTc = QT/RR^{.37}$, fits most datasets fairly well with only a small degree of bias in any one dataset. If one chooses to use this method of correction, we would recommend using the fractional exponent that produces a line with a zero slope in the placebo/baseline data to adjust the on-study QT data.

This method includes the following steps for each exponent tested:

1. Correct the placebo/baseline QT data with the exponent
2. Plot the corrected QT values (using that exponent) against the RR length
3. Calculate the regression line and determine its slope

The exponent generating the slope closest to zero would be selected.

In 1992, Sagie proposed an alternative method for correction after describing the flaws with Bazett's method. We have extended his approach of linear model based correction to randomized studies by fitting a linear model of $QT = a + b \times RR$ to the placebo/unexposed (baseline) study population to adjust the on-study drug group. Using this estimated slope "b", one could then standardize the data for both drug and control treatment groups to a normalized heart rate of 60 bpm (beats per minute) using the following equation:

observed QT(in msec) + [slope (1-RR)] = standardized QT.

One would then proceed with comparing the drug and control experiences. In the 7 datasets that we have examined, this approach worked well.

Since the apparent shape of the QT/heart rate relationship is nonlinear, more complicated models that use nonlinear regression have also been proposed. However, these approaches require sophisticated regression programs and seem to offer little improvement in fit from adjustment based upon a linear model or the fractional exponent method described above.

To summarize, we recommend one of two correction methods be used:

1. identification of the fractional exponent "X" in QT/RR^X that produces a 0 slope with the corrected placebo and/or baseline data plotted against RR
2. the linear model based correction

If you have questions regarding these methods, please contact the Division.

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/s/

Paul David
12/3/01 09:12:09 AM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: October 12, 2001

| | |
|--|---|
| To: Attention: Daniel Coleman, Ph.D. Manager, Regulatory Affairs | From: Paul David |
| Company: Forest Laboratories | Division of Division of Neuropharmacological Drug Products |
| Fax number: 201-524-9711 | Fax number: 301-594-2859 |
| Phone number: 201-386-2126 | Phone number: 301-594-5530 |
| Subject: Request for additional data for pending escitalopram NDA, 21-323 | |

Total no. of pages including cover: 2

Comments: Dan, attached is a request from the OCPB review team for additional information. Please inform me when we might expect to receive these data. Additionally, OCPB would appreciate it if you could fax us the response, and then follow it up with a formal submission to the NDA. Thanks, Paul

Document to be mailed: ☐ YES ☒ NO

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Attachment

Re: Escitalopram 5 mg tablets

Please provide the quantitative and qualitative formulas for the following three batches of the 5 mg tablets. These are: PD 1286; 3384; and 99028C. If this information is contained in the pending NDA, please identify the location - volume and page numbers.

This information in tabular form should have both the milligram amount of each component, as well as its w/w % representation listed alongside. The request is for the 5 mg tablet only.

Please fax your response to Mr. Paul David as well as providing the information as a formal submission, to allow review of the response, as soon as possible. We appreciate your assistance and look forward to your response.

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/s/

Paul David
10/12/01 07:33:23 AM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: July 26, 2001

| | |
|--|---|
| To: Attention: Daniel Coleman, Ph.D. Manager, Regulatory Affairs | From: Paul David |
| Company: Forest Laboratories | Division of Division of Neuropharmacological Drug Products |
| Fax number: 201-524-9711 | Fax number: 301-594-2859 |
| Phone number: 201-386-2126 | Phone number: 301-594-5530 |

Subject: Request for additional data for pending escitalopram NDA, 21-323

Total no. of pages including cover 2

Comments: Dan, attached is a request from the clinical reviewer for additional information. Please inform me when we might expect to receive these data. Thanks, Paul

Document to be mailed: ☐ YES ☒ NO

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Attachment

Our review of your submission is underway. However, we need your assistance in that we have several questions as provided below. If any of the information already exists in the submission please provide the volume, section and page numbers where it can be found. Otherwise please provide us with a response as soon as possible.

Please provide the following:

- A summary of a review of the literature (provide methods employed for the literature search) regarding the safety of citalopram in patients with Major Depressive Disorder and in other patient populations (provide separate summaries for each of these two patient populations). In the summary of this review, please summarize safety information described in articles of placebo-controlled, double-blind studies, a separate summary of the safety information from other types of studies (open label, non-placebo controlled, etc.), a separate summary of safety information from case reports, and a final summary section of safety information obtained from review articles. Please provide a list of the articles generated from the search.
- A listing of the 39 publications found in the literature search on escitalopram that are mentioned in volume 147 page 8-14820 of the submission.
- The number of screened Ss in each study.
- Summary tables of incidence of medical comorbidity (separate tables for current history and if available for past history) for each treatment group for Studies SCT-MD-01 and -MD-02. Please provide summary incidence tables for psychiatric disorders (current history in one table, and if available a table for past history) for each of these two studies.

The following items pertain to the efficacy results of various studies in the submission:

- a. Please provide any and all of your explanations as to why Study MD02 failed to show significant treatment group effects for the LOCF dataset. Also provide your explanations for why Study 99003 which was methodologically similar to MD-02 showed significant effects on the primary efficacy variable for the SCT group and why the CT group failed to show significant effects on the primary efficacy variable (LOCF dataset).
- b. Please conduct gender subgroup statistical analyses (provide descriptive statistical results) for each treatment group on the baseline and treatment endpoint mean score on the primary efficacy variable (of the LOCF dataset) for each of the following studies: Studies MD01, 99001 and 99003.
- c. Please conduct the disease course (single episode and recurrent subgroup categories) subgroup statistical analyses (provide descriptive statistical results) for each treatment group showing results on the baseline, treatment endpoint mean scores and change from baseline to treatment endpoint mean scores on the primary efficacy variable (of the LOCF dataset) for each of the 3 studies mentioned in the above item (b).
- d. Please conduct subgroup analyses by gender and a subgroup analyses by disease course of the LOCF dataset of the primary efficacy variable for each of the 3 studies mentioned in the above item (b) using statistical methods employed for that described in Section 8.0 of the ISE. That is, conduct a gender, treatment, and gender by treatment interaction effects ANCOVA with the baseline score as the covariate for each the 3 studies. Conduct a disease course, treatment and interaction effects ANCOVA with baseline score as the covariate for each of the 3 studies.

We appreciate your response at your earliest convenience. Please let us know when your anticipated turn around time will be. Also please do not hesitate to contact us for clarification. Thank you for your assistance.

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/s/

Paul David
7/26/01 12:00:17 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2001

| | |
|--|---|
| To: Attention: Daniel Coleman, Ph.D. Manager, Regulatory Affairs | From: Paul David |
| Company: Forest Laboratories | Division of Division of Neuropharmacological Drug Products |
| Fax number: 201-524-9711 | Fax number: 301-594-2859 |
| Phone number: 201-386-2126 | Phone number: 301-594-5530 |
| Subject: Request for additional data for pending escitalopram NDA, 21-323 | |

Total no. of pages including cover: 2

Comments: Dan, attached is a request from the statistical reviewer for additional datasets. Please inform me when we might expect to receive these data. Thanks, Paul

Document to be mailed: ☐ YES ☒ NO

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Attachment

Subject: Request for additional datasets for studies SCT-MD-01 & SCT-MD-02

- The NDA contains the efficacy datasets for the studies SCT-MD-01 & SCT-MD-02. In the datasets, the derived values of each primary and secondary efficacy measure scales were included. Please provide the Agency with the raw data sets (i.e., the dataset includes the item responses of each scale) for each study.
- Please provide the Agency with a data set of each study for the dropout patients only. In this data set, keep PAT-ID, TRT-GRP, Time (or visit #) of dropout, Primary reason of dropout, Secondary reasons of dropout (if any).
- Please provide the Agency with the exact SAS codes (including the SAS outputs) so that we can reproduce the reported efficacy results for the primary and secondary outcome measures.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

To: Paul

From: Ohid (Stat. Reviewer) **/S/**

June 22, 2001

Ref: NDA 21-323

Subject: Request for additional datasets for studies SCT-MD-01 & SCT-MD-02

The sponsor submitted the efficacy datasets for the studies SCT-MD-01 & SCT-MD-02. In the datasets, the derived values of each primary and secondary efficacy measure scales were included. FDA Statistician needs the raw data sets (i.e., the dataset includes the item responses of each scale) for each study.

FDA Statistician needs a data set of each study for the dropout patients only. In this data set, keep PAT_ID, TRT_GRP, Time (or visit #) of dropout, Primary reason of dropout, Secondary reasons of dropout (if any).

FDA statistician also needs the exact SAS codes (including the SAS outputs) so that he can reproduce the reported efficacy results for the primary and secondary outcome measures.

**APPEARS THIS WAY
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: September 18, 2001

| | |
|--|---|
| To: Attention: Daniel Coleman, Ph.D. Manager, Regulatory Affairs | From: Paul David |
| Company: Forest Laboratories | Division of Division of Neuropharmacological Drug Products |
| Fax number: 201-524-9711 | Fax number: 301-594-2859 |
| Phone number: 201-386-2126 | Phone number: 301-594-5530 |
| Subject: Request for additional data for pending escitalopram NDA, 21-323 | |

Total no. of pages including cover: 2

Comments: Dan, attached is a request from the clinical reviewer for additional information. Please inform me when we might expect to receive these data. Thanks, Paul

Document to be mailed: ☐ YES ☒ NO

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Attachment

Thank you for your previous response to our questions regarding your submission. Unfortunately, we have not yet received the information we requested regarding results of a literature review on the safety of citalopram, as requested in our 7/26/01 fax. We are hopeful that you can send this information as specified in the 7/26/01 fax, as soon as possible, as it will greatly assist us in the review of your submission. We also need your assistant regarding questions below regarding various aspects of the submission. If the answer to any of these questions already exist in the submission, please provide the volume, section and page number where it can be found, otherwise we look forward to receiving a response as soon as possible or by no later than September 27th. If this date does not allow you sufficient time, please contact us within the next few days. We greatly appreciate your promptness and completeness in your response. If you believe that a conference call would assist in expediting your response to the Agency, please contact Mr. David, and he will make the necessary arrangements.

The number of investigative sites reported in the study reports of the depression trials (MD-01, MD-02, 99001 and 99003) do not match with the number of sites listed in volume 103 sections 8.4.1 and 8.4.2. Please explain the discrepancies and if any investigator information is missing in the tables in sections 8.4, please provide the missing information. Also please provide a statement certifying that all investigators in various listings in the Financial disclosure section of the submission is complete.

Please provide descriptive statistics (mean, standard deviation, median and range) drug exposure for each of the four 8-week depression trials (MD-01, MD-02, 99001, 99003) of subjects in each treatment that completed the study.

Please provide all pertinent clinical information regarding a safety MedWatch report of a death that occurred in an ongoing escitalopram study: Mfr report # T01-FIN-01573-01.

Panel 30 on page 258 (also page 77) of volume 2 of 120-Day Update Report submission shows that 35 placebo, 42 escitalopram and 25 citalopram subjects converted from normal (at baseline) to abnormal (at endpoint) on ECG assessments (for the four depression trials, SCT -MD-01, SCT MD-02, 99001 and 99003, combined). Please provide a line listing of the actual ECG abnormality (rather than simply indicating that it was "abnormal") for each of these subjects of each treatment group. Please organize the line listing by treatment groups for each Study (i.e. a line listing for placebo, escitalopram and citalopram groups for Study MD-01, then provide the same for Study MD-02, etc). If a particular type of ECG abnormality (e.g. bradycardia, tachycardia, nodal arrhythmia, atrial premature contractions, atrial fibrillation, ventricular premature contractions, or with bigeminy, axis deviation, or some other ECG finding) appears in $\geq 1\%$ of a given active treatment group (when combining the four depression trials) then please provide a summary table enumerating the incidence (%) and number of subjects) of that given ECG abnormality.

Please fax your response to Mr. Paul David as well as providing the information as a formal submission, to allow review of the response, as soon as possible. We appreciate your assistance and look forward to your response.

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END=SEP-18 11:41

FILE NO. = 164

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: September 18, 2001

| | |
|--|---|
| To: Attention: Daniel Coleman, Ph.D. Manager, Regulatory Affairs | From: Paul David |
| Company: Forest Laboratories | Division of Division of Neuropharmacological Drug Products |
| Fax number: 201-524-9711 | Fax number: 301-594-2859 |
| Phone number: 201-386-2126 | Phone number: 301-594-5530 |

Subject: Request for additional data for pending escitalopram NDA, 21-323

Total no. of pages including cover: 2

Comments: Dan, attached is a request from the clinical reviewer for additional information. Please inform me when we might expect to receive these data. Thanks, Paul

Document to be mailed: ☐ YES ☒ NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-323

Forest Laboratories, Inc
Attention: Daniel T. Coleman, Ph. D.
Manager, Regulatory Affairs
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for escitalopram oxalate 5 mg, 10 mg, and 20 mg Tablets

We acknowledge receipt of your submission dated March 28, 2001, requesting that the Agency review your proposed tradenames of and Lexapro (secondary).

Our Office of Post-Marketing Drug Risk Assessment (OPDRA) has completed their review of your submission, and they have no objections to the use of the proprietary name, Lexapro.

However, the proposed tradename of is unacceptable for the following reasons:

1. Our primary concerns raised were the sound-alike, look-alike names that already exist in the U.S. marketplace. Such proprietary names include Celexa, Relenza, and Zyprexa.
2. A prescription for may be incorrectly interpreted or transcribed as being Vorexa.

Additionally, OPDRA has the following recommendations pertaining to your submitted labeling and packaging (these comments also pertain to the 10 mg and 20 mg container and carton labeling):

Container Label

1. The proprietary drug name and the established name should be prominent on the label.
2. The established name should be at least ½ the size of the proprietary name in accordance to 21 CFR 201.10(g)(2).
3. The statement "Tablets – 5 mg" is duplicative information and is not necessary.
4. The "5 mg" should appear prominently and differentiated between the other strengths (10 mg and 20 mg). A different color for each strength may be used to highlight the strength of the drug product.
5. The net quantity statement (30 Tablets, etc.) should appear away from the tablet strength. It may be placed under the name and address of the sponsor, in the lower right-hand corner of the label.

6. On the side panel, the statement "See package insert for full prescribing information" should be revised to read "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."
7. On the blister foil, the statement "5 mg" should appear prominently on the label and distinguishable from the other strengths in addition to the statement "Equivalent to 5 mg escitalopram."

Carton Labeling

10 x 10 Blister Box

1. The Back Panel (assuming that this is the main panel) should refer to the above comments (see Container Labeling, Points 1, 2, 4, 5, 6, and 7).
2. The "Rx Only" on the Top Panel should be on the Back (Main) Panel.

8 Boxes x 7 Tablets Blister Box

1. On the 8 boxes x 7 tablets Blister Box, the statement "Rx only - See package insert for full prescribing information" should be revised to state "Rx Only".
2. The Usual Dosage statement should state "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."
3. Please refer to the above comments (see Container Labeling, Points 1, 2, 4, 5, 6, and 7) for the Main Panel.

1 x 7 Blister Box

1. On the Front Panel, please refer to the above comments (see Container Labeling, Points 1, 2, 4, and 7).
2. On the Back Panel, please revise the statement "See package insert for full prescribing information" to state "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."

Please note that this is considered a tentative approval of the tradename. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this letter.

If you have any questions, call Paul David, Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

(See appended electronic signature page)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

9/26/01 09:14:57 AM

**APPEARS THIS WAY
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DA 21-323

DISCIPLINE REVIEW LETTER

Forest Laboratories, Inc
Attention: Daniel T. Coleman, Ph. D.
Manager, Regulatory Affairs
Plaza Three, Suite 602
Jersey City, NJ 07311
USA

Dear Dr. Coleman:

Please refer to your March 21, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Escitalopram oxalate Tablets 5 mg, 10 mg, 20 mg.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

DEFICIENCIES PERTAINING TO DRUG SUBSTANCE:

One

DEFICIENCIES PERTAINING TO DRUG PRODUCT:

Please provide the FDA with a list of the equipment that will be used to manufacture and package Escitalopram oxalate Tablets. Please include a description of the type of equipment, the equipment specifications (i.e., capacity, sieve size, etc.) and at what step in the manufacturing and packaging process the equipment is used.

- Please describe the reprocessing procedures, if any, followed during the manufacture of Escitalopram oxalate Tablets 5 mg, 10 mg and 20 mg.

Please include in method _____, under System Suitability Test, a numerical value for the resolution of the _____.

Please include in the _____ a description of the number of sample injections that should be bracketed with injections of Standard Solution (S1), Working Standard Solution (W_{STD}) and Standard Solution 3 (S3).

BEST POSSIBLE COPY

5. Please include in _____ a description of how the mg Citalopram/Tablet (Assay and Content Uniformity) and % Decomposition Product (w/w) results should be reported for duplicate sample preparation.
6. Please provide the FDA with an explanation for the increase in known and unknown impurities seen in Escitalopram oxalate Tablets packaged in HDPE bottles and blisters stored at 40°C/75%RH and manufactured in the Inwood, NY facility.
7. Please provide the FDA with a statistical evaluation and shelf-life projection, based on the known and unknown impurities, supporting a 24-month shelf-life for Escitalopram oxalate tablets in all package configurations.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products.
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**APPEARS THIS WAY
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/s/

Robert H. SeEVERS
9/4/01 01:32:12 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-323

Forest Laboratories, Inc.
Attention: Daniel Coleman, Ph.D.
Manager, Regulatory Affairs
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Coleman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Escitalopram Oxalate 5 mg, 10 mg, and 20 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: March 23, 2001

Date of Receipt: March 23, 2001

Our Reference Number: NDA 21-323

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 22, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 23, 2002 and the secondary user fee goal date will be March 23, 2002.

We additionally refer to an Agency letter dated March 21, 2001, in which you were informed that FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations until March 1, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call me at (301) 594-5530.

Sincerely,

(See appended electronic signature page)

Paul David, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Paul David

3/28/01 02:02:24 PM

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ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Forest Laboratories, Inc
Attention: Daniel Coleman, Ph.D.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Dr. Coleman:

Please refer to the meeting between representatives of your firm and FDA on November 14, 2000. The purpose of the meeting was to discuss whether the content and the format would be sufficient to submit an NDA for Escitalopram which is the enantiomer of the previously approved racemate, Celexa (citalopram HBr), to treat depression.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Additionally, please note that once the NDA for Escitalopram is filed, you will not be able to amend the application with the efficacy results from your relapse prevention study in depression (number SCT-MD-03). This is clearly stated in the interim guidance document entitled "Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992" otherwise known as the Bundling Policy.

We apologize for any confusion which our previous correspondences may have led you to believe regarding the submission of this data during the course of the review cycle. However, we would fully expect that all of the safety data generated from SCT-MD-03 would be submitted during the course of review.

If you have any questions, call Paul David, Regulatory Project Manager, at (301) 594-5530.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

Date: November 14, 2000
Time: 1:00-2:00 PM, EST
Location: WOC II – Conference Room E
IND: _____
Drug: Escitalopram (LU-26054) 5, 10, and 20 mg Tablets
Indication: Depression
Sponsor: Forest Laboratories
Type of Meeting: Conference Call
Meeting Chair: Thomas Laughren, MD, Psychopharm Team Leader, Division of Neuropharmacological Drug Products (DNDP; HFD-120)
Meeting Recorder: Paul David, R.Ph., Senior Regulatory Manager

FDA Attendees:

Paul David, R.Ph. – Senior Regulatory Manager, DNDP (HFD-120)
Thomas Laughren, MD - Psychopharm Team Leader, DNDP (HFD-120)
Paul Andreason, MD – Clinical Reviewer, DNDP (HFD-120)
Karen Brugge, MD - Clinical Reviewer, DNDP (HFD-120)
Raymond Baweja, PhD – Pharmacokinetics Team Leader, OCPB @ DNDP (HFD-120)
Iftekar Mahmood, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DNDP (HFD-120)
Kun Jin, Ph.D. – Statistical Team Leader, @ DNDP (HFD-120)

Forest Attendees:

Im Abramowitz, PhD – Senior Director, Pharmacokinetics
Robert Ashworth, PhD – Senior Director, Regulatory Affairs
Anjana Bose, PhD – Associate Director, Biostatistics
Daniel Coleman, PhD - Manager, Regulatory Affairs
Charles flicker, PhD – Group Director, CNS Therapeutics Area
Ivan Gergel, MD – VP, Clinical development
Marcello Gutierrez, PhD – Assistant Director, Pharmacokinetics
Julie Kilbane – Associate Director, Project Management
Edward Lakatos, PhD – Senior Director, Biostatistics and Data Management
Charles Lindamood, PhD – Senior Director, Pharmacology and Toxicology
Larry Olanoff, MD –Executive VP, Scientific Affairs

Meeting Objective:

This Pre-NDA meeting was requested by Forest in correspondence dated September 15, 2000, and a briefing package was submitted on October 16, 2000. The primary purpose of this meeting was to discuss whether the content and the format would be sufficient to submit an NDA for Escitalopram, which is the enantiomer of the previously approved racemate, Celexa (citalopram HBr), to treat depression. Specifically, Forest requested feedback on the clinical efficacy/safety, pharm tox, and biopharmaceutics portions of their application. Forest had previously discussed the CMC components with ONDC in a meeting held on April 27, 2000. Forest intends to submit this NDA during the first quarter 2001.

DISCUSSION:

Nonclinical Pharmacology and Toxicology

- Forest's proposed filing plans for the pharm/tox section appear acceptable. . . The Agency previously expressed concern about the cardiac toxicity observed in rats in a 13 week study at a dose of 120 mg/kg Escitalopram. Forest conducted a 60 day rat study with higher doses of

escitalopram to determine whether similar cardiotoxicity findings could be demonstrated for the racemate. Forest intends to submit the data of the cardiotoxicity results for the rat bridging studies this month with the toxicokinetic results data provided in January 2001. The Agency noted that, based upon the results of these studies, we may request additional information prior to approving this drug. This additional information, however, may be submitted during the course of the review.

Human Pharmacokinetics and Bioavailability

- Forest stated that their multiple dose study in the elderly, Study SCTPK-05, would provide the Agency with information that Escitalopram demonstrates linear kinetics similar to the approved racemate form, Celexa.
- The Agency requested information regarding Forest's dissolution program. Forest will submit a comparative dissolution profile in multimedia. Additionally, Forest committed to provide the OCPB group a detailed evaluation of the dissolution program, i.e., three media challenge, bio batches tested, etc.
- Forest's proposed filing plans for the human pharmacokinetics and bioavailability section appear acceptable.

Clinical – Efficacy

- Forest has conducted two studies, one failed study and one positive study. This will be sufficient for filing of the NDA.

Clinical – Safety

- Forest has many ongoing studies; many of which are still blinded. Forest stated that they have roughly 2,000 patients exposed to Escitalopram. However, it is unclear how much safety data will be submitted in the original submission. The Agency is reluctant to review the bulk of the safety data in a 120 day safety update. Forest committed to providing the Agency with a detailed summary of how much information will be submitted in the original application and how much information will be included in the safety update.
- Ideally, the Agency would like to receive individual safety data for each patient of all serious adverse events and patient drop-outs. CRFs by domain are not too useful to the Agency since the reviewer must search through several sections in order to piece one patient together.
- _____

- The Agency questioned whether Forest intended to submit a listing of patient outliers, i.e., clinically significant changes of values such as labs, EKGs, etc. Forest responded that many of the outliers will be captured with the drop-outs and SAEs. The Agency would prefer line listings of all of these patients. Forest committed to submitting a detailed plan on how this data is presented.
- The Agency reminded Forest that we have the right to request CRFs for data only submitted as patient line listings.

Statistical

- The Agency requested that Forest provide the SAS proc contents, with a clear definition of values, prior to the NDA submission. The Agency would then be able to provide Forest with recommendations.

Action Items:

- Forest intends to submit the following information to the Agency: 1) a more comprehensive analysis of how much safety information, including exposure time, that will be submitted with the original NDA and then be updated with the 120 day safety update, 2) the SAS proc contents, and 3) a detailed plan of their dissolution program.
- The Agency will provide Forest with their version of meeting minutes within 30 days of this meeting.

Minutes Preparer

Concurrence, Chair
(or signatory authority)

**APPEARS THIS WAY
ON ORIGINAL**

cc:

HFD-120/Div File
HFD-580/DivFile
HFD-120/R.Katz/T.Laughren/P.Anadreason/K.Brugge
HFD-120/P.David/G.Fitzgerald/P.Roney
HFD-120/R.Seevers
HFD-860/R.Baweja/I.Mahmood
HFD-710/K.Jin
drafted: 11/16/00pd,
final: 12/6/00pd

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Thomas Laughren
12/13/00 10:25:48 AM

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Russell Katz

~ 12/19/00 01:02:27 PM

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THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

11 pages

Office of Drug Safety

MEMO

To: Russell G. Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-400

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

CC: Paul David
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

Date: April 2, 2002

Re: ODS Consult 01-0084-1; Lexapro (Escitalopram Oxalate Tablets); NDA 21-323

This memorandum is in response to a February 27, 2002, request from your Division for a re-review of the proprietary name, Lexapro, and the proposed package insert labeling.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Estrasorb since we conducted our initial review on August 20, 2001 (ODS consult 01-0084), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

Additionally, the proposed package insert labeling was reviewed for safety related issues. A review of the draft insert revealed Lexapro is to be available in three dosage strengths, 5 mg, 10 mg and 20 mg. However, the insert [redacted]. The reviewing medical officer was contacted in an effort to determine the intended use [redacted]. However, further discussion by the reviewing medical officer team is required regarding the necessity from a clinical perspective [redacted].

Therefore, until there is an indication and usage incorporated into the package insert the Division of Medication Errors and Technical Support (DMETS) recommends [redacted] dosage strength. In addition, "Lexapro" should be inserted for the "Name of Product" in the Special Population subsection of the Dosage and Administration section.

The Division of Medication Errors and Technical Support (DMETS) considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Scott Dallas
4/3/02 08:10:46 AM
PHARMACIST

Carol Holquist
4/3/02 01:29:24 PM
PHARMACIST

**APPEARS THIS WAY
ON ORIGINAL**



NDA 21-323

Forest Laboratories, Inc.
Attention: Robert W. Ashworth, Ph.D.
Senior Director, Regulatory Affairs
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Ashworth:

We acknowledge receipt on February 21, 2002 of your February 20, 2002 resubmission to your new drug application (NDA) for Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg tablets.

This resubmission contains additional information submitted in response to our January 23, 2002 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is August 21, 2002.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

January 7, 2002

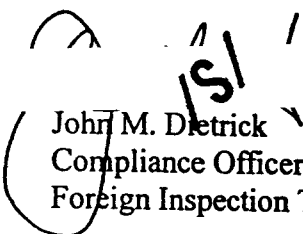
Dear _____

We have completed review of your October 30, 2001 letter and documentation submitted in response to our letter of August 9, 2001 following the inspection conducted at your active pharmaceutical ingredient facility in _____ by FDA Investigator Marybet Lopez and Chemist Margarita Santiago. The documentation submitted appears to provide satisfactory correction for the remaining concern regarding the investigation of OOS assay results. Based on this response we are classifying your facility as acceptable as the supplier of Escitalopram Oxalate API for the pending New Drug Application.

The corrective actions taken will be further evaluated during the next inspection of this facility. It remains your responsibility to assure compliance with current good manufacturing practices.

You may contact me at 7520 Standish Place, HFD-322, Rockville, MD 20855. You may also contact my office by telephone at (301) 594-0095 or by fax at (301) 594-1033.

Sincerely,


John M. Dietrick
Compliance Officer
Foreign Inspection Team, HFD-322

LAST PAGE

OF

Approval Package
